pathic lesions which so destroy the quality of the diabetic patient's life.

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Role of pH-dependent bile acid precipitation in fat maldigestion due to pancreatic steatorrhoea. Preliminary communication

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Key words: PANCREATIC DISEASES; STEATORRHOEA; CYSTIC FIBROSIS; BILE ACID PRECIPITATION

Summary

In pancreatic steatorrhoea due to cystic fibrosis (CF) a major proportion of the meal enters the jejunum below the critical pH of 5, causing bile acid (BA) precipitation and limiting aqueous solubilisation of lipid. Treatment with pancreatin alone results only in a small increase in lipolysis as the lipase is largely inactivated; aqueous lipid solubilisation is not improved as BA precipitation remains a limiting factor. Treatment with cimetidine alone, by reducing BA precipitation, improves lipid solubilisation without improving lipolysis. Treatment with cimetidine and pancreatin reduces pancreatic lipase inactivation and BA precipitation leading to the greatest improvement in lipid solubilisation.

Introduction

Steatorrhoea due to pancreatic exocrine insufficiency can lead to severe malnutrition and socially embarrassing symptoms. It often responds poorly to treatment with pancreatic enzyme supplements and many patients take 10 or more pancreatin tablets with each meal. Inactivation of pancreatic enzyme supplements by gastric acid has been demonstrated and provides one explanation for the failure of pancreatin therapy. The purpose of this study was to determine whether bile acid deficiency also contributes to fat maldigestion.

Our hypotheses were that diminished pancreatic bicarbonate secretion would lead to a reduction in the postprandial jejunum pH and thus to bile acid (BA) precipitation, since glycine-conjugated BAs precipitated in vitro below pH 5. BA precipitation would lead to a reduction in BA concentration in the aqueous phase of intestinal contents, and a reduction in aqueous solubilisation of lipid might result.

Untreated study: comparison with health

In order to test these hypotheses we have studied 12 adults with steatorrhoea due to cystic fibrosis (CF) and 14 healthy adult controls (HC). After an overnight fast a double-lumen tube was passed to the duodenojejunal flexure. A Lundh-type meal containing polyethylene glycol 4000 (PEG) as a non-absorbable meal marker was given, without pancreatin tablets. Samples were aspirated continuously for 3 h. The pH was measured immediately in each 4-ml sample, which was then allocated to the appropriate one of three pH pools (<5, 5–6, >6) and treated to arrest lipolysis. Each of these pH pools was later analysed for total saponifiable lipid, fatty acid, BA, trypsin, lipase, and PEG. An aliquot from each pool was ultracentrifuged overnight at 100 000 G to separate the aqueous phase, which was removed and analysed for saponifiable lipid, fatty acid, and BA. Statistical analysis was performed by the paired or unpaired Wilcoxon test as appropriate.

Our results demonstrated that twice as much of the meal, estimated by PEG recovery, entered the jejunum below the critical pH of 5 in CF than in HC (mean 38.2% in CF *v* 17.7% in HC; $p<0.05$). Total BA concentration was significantly higher in CF than in HC, but 45.7% of the BAs were precipitated at pH<5 in CF compared with 14.5% at pH>6 ($p<0.01$). This led to a marked reduction in aqueous-phase BA concentration at low pH (4.7 mmol/l at pH<5 *v* 12.5 mmol/l at pH>6; $p<0.01$), which in turn was associated with a marked reduction in aqueous-phase lipid concentration (5.6 *v* 10.2 mmol/l; $p<0.01$) and fatty acid concentration (0.9 *v* 2.6 mmol/l; $p<0.01$). In all cases the values for pH 5–6 were intermediate. The presence of apparent BA precipitation at pH>6 can be attributed to binding of BA to undigested protein in the meal, which we have demonstrated in vitro.

Lipase and fatty acid concentrations were very low in CF. Since they did not vary with pH in the whole sample, the reduction in lipid and fatty acid concentration in the aqueous phase at pH<5 can be attributed to the limiting

effect of BA precipitation on aqueous-phase lipid solubilisation.

In HC similar pH gradients were observed but were quantitatively less important as only 17% of the meal entered the jejunum at pH<5. In addition, lipase concentration was reduced at low pH (133 U/l at pH<5 *v* 182 U/l at pH>6; p<0.01), leading to significant pH gradients for lipolysis and total fatty acid concentration. This indicates that in health pancreatic enzymes are inactivated in vivo at pH<5.

Treatment study

These results suggest that jejunal acidification is important in fat maldigestion. Cimetidine, by reducing gastric acid secretion, might raise postprandial jejunal pH and thus prevent BA precipitation in addition to preventing inactivation of pancreatic enzyme supplements, thus improving lipid solubilisation. In order to investigate this hypothesis we have repeated jejunal aspiration in 7 patients with CF using an identical technique. Three therapeutic regimens were given in random order on separate occasions: (1) pancreatin alone (7 Pancrex V capsules with the meal); (2) cimetidine alone (400 mg given 40 min before the meal); (3) cimetidine plus pancreatin. Comparison of these three regimens with the untreated regimen would indicate whether prevention of BA precipitation or of pancreatin inactivation played a greater part in the known effect of cimetidine in reducing faecal fat excretion in pancreatic steatorrhoea.

On treatment with pancreatin alone a mean of 59% of the meal was aspirated at pH<5, again demonstrating the marked jejunal acidification in CF. On the two cimetidine regimens the entire meal was aspirated at pH>6, demonstrating successful control of jejunal acidification.

Treatment with pancreatin alone resulted in a small but significant increase in lipase (15.1 *v* 3.7 U/l; p<0.01) and in lipolysis (12.5 *v* 8.8%; p<0.05) compared with no treatment. BA precipitation was unaffected and aqueous-phase lipid concentrations did not rise in comparison with no treatment. Thus BA precipitation appears to limit solubilisation of lipids during treatment with pancreatin just as it does in the untreated patient. This interpretation is supported by the increased BA precipitation and reduced lipid solubilisation at pH<5 compared with pH>6 on treatment with pancreatin alone, similar to the pH gradients demonstrated on no treatment.

Treatment with cimetidine alone resulted in significantly higher aqueous-phase lipid concentrations than with pancreatin alone (9.0 *v* 6.4 mmol/l; p<0.05), despite significantly less lipolysis (6.2 *v* 12.5%; p<0.05) and no increase in lipase. This again suggests that reduction in BA precipitation alone can improve lipid solubilisation. BA precipitation was markedly reduced on treatment with cimetidine alone compared with pancreatin, although the difference was not significant (mean ± SEM, 17.8 ± 3.8% *v* 31.3 ± 10.1%; NS). Treatment with pancreatin plus cimetidine demonstrated that prevention of pancreatin inactivation achieved a further improvement in lipid solubilisation. Lipase increased markedly with the addition of cimetidine to pancreatin (40.5 *v* 15.1 U/l; p<0.01), as did lipolysis (19.7 *v* 12.5%; p<0.05). BA precipitation was significantly reduced by the combination in comparison with pancreatin alone (4.3% *v* 31.3%; p<0.01). As a result of both effects (improved lipolysis and reduced BA precipitation) there was a considerable increase in aqueous-phase lipid concentration over pancreatin alone (18.8 *v* 6.4 mmol/l; p<0.05). Aqueous-phase lipid concentration was also increased by the combined regimen in comparison with cimetidine alone (18.8 *v* 9.0 mmol/l; p<0.05). This was associated with a marked trend to a reduction in BA precipitation (4.3 ± 6.2% *v* 17.8 ± 3.8%; NS). This cannot be attributed to pH-dependent precipitation since pH was maintained above 6 on both regimens; it may result from improved digestion of protein causing reduced protein-binding of BA.

Conclusion

We conclude that pH-dependent BA precipitation limits aqueous solubilisation of lipid in pancreatic steatorrhoea due to CF and that for optimum therapy BA precipitation, as well as pancreatic enzyme inactivation, must be prevented.

FREE PAPERS

The role of surgery in the management of chronic pancreatitis

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A total of 39 patients have undergone surgical treatment for chronic pancreatitis or its immediate complications out of 240 patients referred for assessment. Of those submitted to surgery 25 were male and 14 female (age range 12–58, mean 38 years). Thirteen had undergone previous pancreatic surgery prior to referral. Alcohol abuse was the most common aetiology (n = 23), while biliary disease and trauma were associated factors in a further 10 patients. Severe abdominal pain was present in all but 1 and this was the major indication for surgical treatment in most patients. Six had biliary tract obstruction due to compression of the lower common bile duct, while 5 had a pancreatic cyst or fistula and in 1 patient duodenal obstruction was present.

A total of 42 operations were performed. Hospital mortality was 4.9% (2 patients) and 2 late deaths have occurred, 1 being unrelated to chronic pancreatitis. Follow-up extends from 1 to 10 (mean 3.4) years. In 26 patients a good result has been obtained, while 5 only continue to be troubled by pain. In 4 patients diabetic control is intermittently troublesome and a further patient is troubled by occasional severe diarrhoea.

Morphometry of the exocrine pancreas

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It has been suggested that the increased incidence of pancreatic adenocarcinoma in the pancreatic head re-

flects a greater tissue mass in the head *(1)*. Alternatively Bates *(2)* has postulated a difference between tissue arising from the embryological ventral bud (confined to head) and the dorsal bud. Two questions arise: (1) What is the distribution of tissue between pancreatic head and body? (2) Does either the concentration of ductal and acinar tissue or the distribution of duct size vary?

The weights of the head and neck and the body and tail of postmortem pancreata were measured. Sections were taken from the head ('dorsal and ventral' portions) and the body. The concentration of ductal and acinar tissue and the total duct perimeter were measured by light microscopy and computerised morphometry. Results were analysed by Student's test and were as follows:

1) The mass of tissue (25 pancreata) in the head and neck was less than in the body and tail ($p<0.001$).

2) There was no significant difference throughout the pancreas (10 pancreata) in duct concentration, total perimeter of ducts per section, or distribution of duct size.

It was concluded that there is more ductal and acinar tissue in the body and tail of the pancreas and there is no structural difference between the 'ventral' and 'dorsal' pancreas. This suggests that the distribution of pancreatic adenocarcinomas may not be uniform throughout the pancreas.

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THE 50TH ANNIVERSARY OF THE ROYAL COLLEGE OF PHYSICIANS AND SURGEONS OF CANADA

The fiftieth Annual Meeting of the Canadian College was held at the Harbour Castle Hotel at Toronto during the week of 14th September 1981 under their President Dr Bernard J Perey. The meeting was well attended and multidisciplinary and, on account of the special occasion, Presidents or their deputies from the Royal Colleges in the UK and Australasia, the College of Surgeons and Physicians of South Africa, and from the College of Surgeons of the neighbouring United States attended.

Before we arrived the Canadian postal strike had been an inconvenience, but the efficient organising team of Drs Delarue Fallis and Darragh with their wives and colleagues made this look as though it had never occurred. On every day there was an active scientific programme with something of interest for everyone, whether he be generalist or specialist physician or surgeon. The Gallie Memorial Lecture was given by Dr Hiram C Polk Jr, who is Chairman of the Department of Surgery at the University of Louisville, Kentucky. He lectured on 'Infection in the surgical patient'. The ladies fared equally well.

A special vote of thanks must be given to the Toronto doctors and their wives who acted as special hosts to the College visitors, meeting them at the airport, looking after them, and making sure that they got away safely.

There were many aspects of the meeting which, as a visitor from the English College, gave me a happy feeling of déjà vu. This was particularly true of the Convocation ceremony, which is so like our own diploma ceremony at the College. With the President leading, the platform party, which included Canadian College Officers and their guests, processed to the hall. Their Surgical Vice-President carried the College mace — a gift to them from our Royal College. The Physician Vice-President carried the Caduceus, a symbol of the office of President and a gift from the Royal College of Physicians of London.

We entered the hall to the music of the 48th Highlanders of Canada.

After the Canadian National Anthem new Fellows in Medicine and Surgery were presented to the President by the Vice-Presidents — the physicians by Dr Ross Langley and the surgeons by Dr William M Paul — at the rostrum. Each received a hearty surgical handshake and a word of congratulation.

Then Drs Bruce Chown, of Victoria, Canada, and Dr Bryan Hudson, of Melbourne, Australia, were introduced and admitted to the Honorary Fellowship. Following this the Graham Duncan Award was presented to Dr Donald Wilson, of Edmonton, for his contributions to postgraduate medical education.

Dr Charles H Hollenberg, Professor and Chairman of the Department of Medicine in the University of Toronto, gave the address to the new Fellows. His approach was realistic and challenging, pointing out the chances and problems of medicine in Canada.

The ceremony ended with 'God Save the Queen', followed by a reception for the new Fellows.

I was particularly pleased to meet two old friends of our College and Past Presidents of the Canadian College — Robert Salter, of Toronto, and Charles Drake, of London, Ontario. Many of us will remember them when they were Sims Travelling Professors. Dr Salter was also chairman of a group of contributors who have produced a most attractive book on the history of the Canadian College.

We all like occasions of ceremony and an anniversary is always something special. I am sure that all the Fellows of our College join me in wishing our sister College in Canada good fortune for a future which has started so well.

G J HADFIELD CBE TD FRCS